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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FORD, ALLISON M	
ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 07/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/675,938	RATHJEN ET AL.	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-15 and 36-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-15 and 36-38* is/are rejected.

7)☒ Claim(s) *1 and 10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments/Amendments

Applicant's arguments filed 25 April 2005 have been fully considered but they are not persuasive. Amendments to claims 1 and 4-7 have been entered. New claims 36-38 have been added. Claims 3 and 16-35 have been cancelled. Claims 1, 2, 4-15 and 36-38 are pending in the current application.

Priority

Acknowledgement is made of applicant's claim for priority to provisional application 60/414,959, filed 9/30/2002.

Claim Objections

Applicant has provided the full terms "embryonic stem cell" and "early primitive ectoderm-like" cells before the abbreviations ES and EPL, respectively. However, in amended claim 1 applicant uses the abbreviation EB to refer to "embryoid bodies;" however, in claim 10 the abbreviation EBMs is used to refer to "embryoid bodies" the same abbreviation must be used throughout the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 36 and dependent claims 2, 4-9 and 37-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. See MPEP § 2136.

Applicant's amended claim 1 is directed to a method for directing a population of embryonic stem cells to differentiate to mesodermal tissue, said method comprising culturing said embryonic stem cells in the presence of a medium in which said cells will partially differentiate into early primitive ectoderm-like (EPL) cells; culturing said EPL cells in suspension culture, thereby forming EPL embryoid bodies (EB); culturing the EB in the presence of bone morphogenic protein 4 (BMP4) or a functional equivalent thereof for a time and under conditions sufficient for cells within the EB to preferentially differentiate into said mesodermal tissue.

Applicant teaches using bone morphogenic protein 4 (BMP4) to induce differentiation of mouse ES cells into cells of mesodermal lineage (See Specification, Pg. 25-27). However claim 1 is drawn to BMP4 or a functional equivalent thereof. There is insufficient written description provided in the disclosure to adequately describe the BMP4 used in the experiment, as they do not disclose the species of origin, therefore there is complete lack of written description to sufficiently describe homologues functional equivalents thereof. It is understood that mouse and human BMP4 are over 98% homologous and functionally equivalent (R&D Systems), however applicant has failed to disclose the relevant, identifying characteristics by their functional components, of all BMP4s and functional equivalents thereof, to sufficiently show the applicant was in possession of the entire scope of the claimed genus: BMP4. *See Eli Lilly,* 119F. 3d. at 1568, 43 USPQ2d at 1406.

Applicant's claim 36 is directed to a method for directing a population of cells of mesodermal lineage to differentiate into mesodermal tissue, said method comprising culturing cells of mesodermal lineage in the presence of bone morphogenic protein 4 (BMP4) for a time sufficient for said cells to preferentially differentiate into mesodermal tissue. Claim 2 requires the cells to be early primitive ectoderm-like cells (EPL cells). Claim 4 requires the cells of mesodermal lineage to be selected from the

group consisting of somatic stem cells, germ stem cells, adult renal stem cells, embryonic renal epithelial stem cells, embryonic endodermal stem cells, hepatocyte stem cells, mammary epithelial stem cells, bone marrow-derived stem cells, skeletal muscle stem cells, bone marrow mesenchymal stem cells, $CD34^+$ haematopoietic stem cells, and mesenchymal stem cells.

Applicant describes the method by which they induced mouse embryonic stem cells to differentiate into cardiomyocytes in the presence of BMP4 (See Specification, Pg 25-27). They have not, however, provided sufficient written description to enable for any cell type of mesodermal lineage (Claim 36) or even for the types of stem cells listed in claim 4. The embryonic mouse cell is the only example given, embryonic stem cells are not cells of mesodermal lineage; therefore it does not constitute a single example of cells of mesodermal lineage, much less a representative number of species of cells of mesodermal lineage required to claim the entire genus. One skilled in the art recognizes cells differ immensely, for example terminally differentiated cells are very different then embryonic stem cells. The embryonic mouse cell is not even representative of the list of stem cells in claim 4. The types of stem cells listed in claim 4 includes what would more appropriately be called progenitor cells, they have undergone several steps of differentiation; for example, hepatocyte stem cells have undergone partial differentiation directed towards becoming hepatocytes, they do not have the same totipotency as embryonic stem cells, which have the potential to become ectoderm, endoderm or mesoderm cells. The different stem/progenitor cells have different receptors and different pathways; they would react differently to the same stimulus, including BMP4. For example, Finley et al teach that BMP4 only directs cells towards mesodermal lineage differentiation during a restricted time period from day 5-8 (See Finley et al, Pg 277, col. 2- Pg. 278, col.2 and Table 1); therefore an adult renal stem cell, which has partially differentiated and thus is pass day 8 of differentiation, would not have the same reaction to BMP4 as an embryonic stem cell at day 5 of differentiation. Additionally, there is no disclosure of relevant, identifying characteristics, such as the particular receptor or pathway required in the cell to be affected by

BMP4, sufficient to show the applicant was in possession of the claimed genus. *See Eli Lilly,* 119F. 3d. at 1568, 43 USPQ2d at 1406.

Claim 36 and dependent claims 4-9 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of directing a population of undifferentiated cells mesodermal lineage to differentiate into mesodermal cells, does not reasonably provide enablement for a method of directing any population of cells of mesodermal lineage to mesodermal tissue. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Only undifferentiated cells can be induced to differentiate, therefore the method is limited to stem cells and progenitor cells of mesodermal lineages, terminally differentiated cells of mesodermal lineage, such as mature hepatocytes, cannot be induced to differentiate.

Applicant has amended claim 1 to be a method for the directed differentiation of embryonic stem cells to mesodermal tissue; thus overcoming the written description rejection of claim 1 that the genus of "cells" is too broad.

However, the broad genus of "cells" has been re-written in only slightly narrower form in new claim 36. Claim 36 is directed to a method of directing a population of cells of mesodermal lineage to differentiate into mesodermal tissue. Applicants have provided one example of directing embryonic stem cells to form EPLs in MEDII medium, allowing the EPLs to aggregate to form EBMs and culturing the EBMs in presence of BMP4, resulting in differentiated cardiomyocytes (See spec, Pg 25-27). However, the new claim is rejected as lacking written description for all cells of mesodermal lineage, and lacking enablement for all cells of mesodermal lineage. Embryonic stem cells are not cells of mesodermal lineage, they are capable of giving rise to cells of mesodermal lineage, as well as cells of ectodermal and

endodermal lineages; therefore, applicant has not provided a single example of directing a population of cells of mesodermal lineage to differentiate into mesodermal tissue. Within the genus of "cells of mesodermal lineage" are included many more non-progenitor cells types, such as terminally differentiated cells (mature hepatocytes, myocytes, etc) which have not been described in the disclosure, and are not represented or enabled by the sole example of an embryonic stem cells. The types of stem cells listed in claim 4 includes what would more appropriately be called progenitor cells, they have undergone several steps of differentiation; for example, hepatocyte stem cells have undergone partial differentiation directed towards becoming hepatocytes, they do not have the same totipotency as embryonic stem cells, which have the potential to become ectoderm, endoderm or mesoderm cells. The different stem/progenitor cells have different receptors and different pathways; they would react differently to the same stimulus, including BMP4. Therefore, while applicant has enabled for the directed differentiation of embryonic stem cells, they have not enabled for the directed differentiation of any stem/progenitor cell, and certainly not for any cell of mesodermal lineage.

Claim Rejections – 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15 and 36-38 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's claim 1 is directed to a method for directing a population of embryonic stem cells to differentiate to mesodermal tissue, said method comprising culturing said embryonic stem cells in the presence of a medium in which said cells will partially differentiate into early primitive ectoderm-like (EPL) cells; culturing said EPL cells in suspension culture, thereby forming EPL embryoid bodies (EB);

culturing the EB in the presence of bone morphogenic protein 4 (BMP4) or a functional equivalent thereof for a time and under conditions sufficient for cells within the EB to preferentially differentiate into said mesodermal tissue.

Applicant's claim 36 is directed to a method for directing a population of cells of mesodermal lineage to differentiate into mesodermal tissue, said method comprising culturing cells of mesodermal lineage in the presence of bone morphogenic protein 4 (BMP4) for a time sufficient for said cells to preferentially differentiate into mesodermal tissue.

It remains unclear what constitutes sufficient time and conditions for differentiation of cells into mesodermal cells or cells of a mesodermal lineage to occur. Furthermore, the term 'preferentially' makes it unclear if it is required that the cells differentiate into mesodermal cells or cells of a mesodermal lineage, or if it is only preferred.

Applicant's claim 10 is directed to a method for generating mesodermal cells from ES or EPL cells, comprising culturing ES cells or EPL cells in MEDII or its functional equivalent in order to generate embryoid bodies; maintaining EBMs in culture for a time sufficient to allow aggregation of said EBMs; transferring aggregated EBMs to gelatin-treated wells; allowing said aggregated EBMs to adhere to gelatin-treated wells; and culturing adhered EBMs in serum free medium comprising BMP4 for a time sufficient to allow EBMs to generate mesodermal cells, and thereby generate mesodermal cells from ES cells or EPL cells.

It remains unclear how ES cells *or* EPL cells are cultured in MEDII; EPL cells are formed *by* culturing ES cells in MEDII (See Lake et al, Pg. 556, col. 1).

With regards to the rejection of claims 1, 36 and dependent claims 2, 4-9 and 37-38, applicant's remarks state that claim 1 has been amended to remove the indefinite terms "conditions" and

"preferentially" but both terms persist in claim 1, and "preferentially" is also present in new claim 36. Therefore the claims have not been amended and the rejection remains.

With regards to the rejection of claim 10 and dependent claims 11-15, applicant argues that even when ES cells have been formed by culture they require extra time for aggregation as part of the differentiation process. Embryonic stem cells are not formed by culture; rather the EPL cells are formed by culturing ES cells in the MEDII medium (See Lake et al, Pg. 556, col. 1). Formation of the EPL cells from ES cells is critical to the invention (See applicant's response, pg. 9); therefore the method requires culturing ES cells *to form* EPL cells, and then further culturing the EPL cells in MEDII medium to form embryoid bodies. Applicant does not disclose how to form or otherwise obtain EPL cells except from ES cells; therefore it remains unclear how the method of claim 10 is carried out by culturing EPL cells in MEDII.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4-15 and 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lake et al (*Journal of Cell Science*, 2000), in view of Schuldiner et al (*PNAS*, 2000), in light of information from Dr. Benvenisty (of Schuldiner et al), Finley et al (*J Neurobiology*, 1999), and Johansson et al (*Mol. Cell. Biol.*, 1995).

Lake et al teach culturing mouse ES cells (D3 line) in ES DMEM containing 50% MEDII, without LIF, to produce EPL cells. Embryoid bodies (what applicant refers to as EBMs, embryoid bodies produced in MEDII) were formed from a single EPL cell suspension plated at 1×10^5 cells/ml in

bacteriological grade dishes in ES DMEM. With the exception of Lake et al using ES DMEM instead of DMEM conditioned with 50% MEDII during the aggregation of EPL cell embryoid bodies, and the transfer of aggregated EBs to gelatin-treated wells, the process by which Lake et al formed EPL cell EBs is identical to the process of forming EBMs in the current application (See Lake et al, Pg 556, col. 2; See Specification, Pg. 25-26). The culturing of EPL cell EBs in DMEM, as opposed to DMEM conditioned with 50% MEDII does not appear to have a significant effect on the cells; EPL cells were already formed, and only reverted back to ES cells in the presence of LIF (See Lake et al, Pg 556, col.2). Therefore the continued use of DMEM conditioned with 50% MEDII during the aggregation of embryoid bodies appears to be an obvious design choice and does not have an affect on the morphology of the embryoid bodies formed. Similarly, transferring the EPL cell EBs to gelatin-treated wells is one method of culturing EBs; Lake et al chose to culture the EBs in a suspension culture. Both techniques are acceptable forms of culturing EBs, as neither shows any improvement or advantage over the other method, therefore the technique of culturing EBs is another an obvious design choice based on personal preference and material availability. Therefore Lake et al teach the same process of forming embryoid bodies as in the current application, and thus the EPL cell EBs formed by Lake et al are one and the same as the EBMs formed in the current application.

Lake et al continued to assess the EPL cell EBs' ability to differentiate by monitoring expression of *brachyury* and appearance of beating cardiocytes (which applicant calls cardiomyocytes) (See Lake et al, Pg 560). The EPL cell EBs did differentiate into mesodermal cells, as evidenced by 60% of cells showing beating muscle by day 6, and a 30-fold increase in expression of *brachyury* on days 2 and 3 (See Pg. 556, col. 2). However, others teach culturing EBs in the presence of BMP4 increases the degree of differentiation into mesodermal cells. Schuldiner et al teach culturing human EBs in presence of human BMP4 induced differentiation into mesodermal cells, such as chondrocytes and blood cells (See Schuldiner et al, Pg. Pg 11307, col. 2- Pg 11308, col. 1; Pg 11311, col. 1; & Fig. 4; See Information from

Dr. Benvenisty). Finley et al teach treating aggregates (what applicant calls embryoid bodies) with BMP4 (source species unknown) significantly reduced generation of neural and glial cells (ectodermal lineage) and increased generation of cells of mesodermal lineage, evidenced by morphology, presence of vimentin (an intermediate filament protein expressed by early-migrating mesodermal and mesenchymal cells), and an increase in expression of *brachyury* (See Finley et al, Pg. 273, col. 1; & Pg. 278, col. 2- Pg. 281, col. 1). Finally, Johansson et al teach mouse ES cells cultured in chemically defined media form EBs and will exhibit low levels of spontaneous mesoderm formation, due to factors synthesized by the ES/EBs themselves; however, mouse EBs cultured in presence of human BMP4 show increased differentiation into mesodermal cells, evidenced by enhancement in formation of cardiac muscle formation (See Johansson et al, Pg 142, col. 1; Pg. 145, col. 1-2; 147, col. 1- Pg 149, col. 1).

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to culture EPL cells EBs (what applicant calls EBMs) in the presence of BMP4 in order to generate cells of mesodermal lineage. The person of ordinary skill in the art would have been motivated to generate mesodermal cells by this method in order to increase control over the differentiation pathway of the ES cells. One would expect success because Lake et al teach that EPL cells have a distinct morphology that predisposes them to formation of mesodermal lineages, and Schuldiner et al, Finley et al, and Johansson et al teach that directed differentiation towards mesoderm is increased when EBs are treated with BMP4; therefore treating cells predisposed to the mesodermal lineage with a growth factor that stimulates differentiation into the mesodermal lineage would be expected to produce mesodermal cells.

Therefore Lake et al, in view of Schuldiner et al, Finley et al, and Johansson et al teach a method of generating mesodermal cells by culturing D3 cells (mouse ES stems), in MEDII to form EPL cells, aggregating the EPL cells into EPL cell EBs (what applicant calls EBMs), culturing the EPL cell EBs

(EBMs) in presence of human BMP4 for a time sufficient to allow differentiation of EPL cell EBs into mesodermal cells.

Additionally, though Johansson et al teach culturing the mouse ES stem cells in human BMP4, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use mouse BMP4 or human BMP4 (Claims 5 & 6). One would have been motivated to alternatively use mouse BMP4 in order to optimize experimental conditions, since mouse ES cells were used. One would have expected success using either mouse or human BMP4 because they are 98% homologous and R&D Systems teaches they can be used interchangeably, and Johansson et al has shown BMP4 does induce differentiation of ES cells into mesodermal lineages (See Pg 273, col. 1-2 and See Pg 278, col. 2- Pg. 281, col. 1).

Lake et al use mouse embryonic stem cells and EPL cells formed from the mouse ES cells. They do not experiment with cells of mesodermal lineage (claim 36), such as those stem/progenitor cells in claim 4, or any other type of cells from animals, such as those listed in claims 7, 8, 13 and 14, nor do they use human cells (claims 9 and 15). However, at the time the invention was made Lake et al, in view of Schuldiner et al, Finley et al, and Johansson et al, taught the same steps performed by applicant, including use of the same cell line (D3 ES cell line) (See Lake et al, Pg 556, col. 2; See Specification, Pg. 25), but applicant extrapolates broader claims, including use of various types of stem/progenitor cells of mesodermal lineage, such as those listed in claim 4, cells from animals, such as those listed in claims 7 and 13, and use of human cells, without further experimental evidence. Therefore, applicant's actual induction of practice is the same as that taught by Lake et al, in view of Schuldiner et al, Finley et al, and Johansson et al, therefore Lake et al, in view of the others, was equally enabled as applicant for the directed differentiation of cells of mesodermal lineage (claims 4 and 36), all types of animal cells (claims 7, 8, 13 and 14), and human cells (claims 9 and 15). And thus the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicant argues that Lake et al do not teach culturing the EPLs in the presence of BMP4, rather Lake et al only teach that EBs (EPLs formed in MEDII) have a distinct morphology that predisposes them to formation of mesodermal lineages, as evidenced by 40-60% of the EBs differentiating into mesodermal cells in the form of cardiomyocytes (See Lake et al, Pg. 556, col. 2); furthermore, applicant's argue that the secondary teachings of Johansson et al, Schuldiner et al and Finley et al do not suggest that exposure of EBs to BMP4 would increase the percentage of cells differentiated into mesodermal tissue, but would actually decrease the percentage. Applicant's base the expectation of a decreased percentage of cells differentiated into mesodermal lineage on the fact that Johansson et al teach that 20-40% of cells produced from embryoid bodies exposed to BMP4 were of mesodermal lineage. Because Johansson et al teach only 20-40% of the cells produced from embryoid bodies exposed to BMP4 were of mesodermal lineage, while Lake et al show 40-60% of the cells produced from embryoid bodies cultured in MEDII formed cells of mesodermal lineage, applicant's feel that the teachings of Johansson et al would suggest a decrease in the formation of cells of mesodermal lineage.

The examiner maintains that one of ordinary skill in the art would be motivated to combine the teachings of Lake et al, who teach embryoid bodies formed from EPL cells in MEDII have distinct morphologies that dispose them to formation of mesodermal lineages, with the teachings of Johansson et al, Schuldiner et al and Finley et al, who teach that exposure of embryoid bodies to BMP4 increases the rate of different ion to cells of mesodermal lineage, to expose embryoid bodies formed from EPL cells in MEDII to BMP4 in order to direct differentiation to cells of mesodermal lineage. One would have had a reasonable expectation of successfully increasing the percentage of cells directed to differentiate into mesodermal lineage by combining two methods known, individually, to increase the percentage of cells directed to differentiate into mesodermal lineage. Combining two methods that have the same effect would have an additive effect, thereby forming a single, third method with the same effect intensified.

See *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). Johansson et al, Schuldiner et al and Finley et al all show that exposure of embryoid bodies to BMP4 increases the percentage of cells directed to mesodermal lineages. Johansson et al report an increase of 20-40% of cells directed to mesodermal lineage; though Schuldiner et al and Finley et al do not report percentages of increased directed differentiation to cells of mesodermal lineages, they both teach increased differentiation to cells of mesodermal lineages. One of ordinary skill in the art would expect an additive effect in combining the two methods (forming EBs from EPLs in MEDII (Lake et al) and exposing EBs to BMP4 (Johansson et al, Schuldiner et al and Finley et al)), not a reduction in percentage equal to the average between the percentages found by Lake et al and Johansson et al. Therefore Lake et al, in view of Schuldiner et al, Finley et al, and Johansson et al teach a method of generating mesodermal cells by culturing D3 cells (mouse ES stems), in MEDII to form EPL cells, aggregating the EPL cells into EPL cell EBs (what applicant calls EBMs), culturing the EPL cell EBs (EBMs) in presence of human or mouse BMP4 for a time sufficient to allow differentiation of EPL cell EBs into mesodermal cells.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M Ford whose telephone number is 571-272-2936. The examiner can normally be reached on M-F 7:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0927. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Allison M Ford
Examiner
Art Unit 1651

LEON B. LANKFORD, JR.
PRIMARY EXAMINER